REMARKS

Claims 1-29, 35, and 37-48 were pending in the application. Claims 1, 2, 39, 40, and 46 have been amended to clarify the invention. Support for the amendment of claims 1, 2, 39, 40 and 46 may be found throughout the specification and claims as originally filed. For example, support for the amendment to claims 40 and 46 may be found at least at page 4, lines 13-14. No new matter has been added.

Accordingly, upon entry of the present amendment, claims 1-29, 35, and 37-48 will be pending. Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The cancellation of and/or amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application.

Applicants gratefully acknowledge that the Examiner found claims 24-28 and 39 to be allowable and claims 6-8 and 12-23 to be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims.

Rejection of Claims 35-38, 42-48 under 35 U.S.C. § 112, first paragraph

Claims 35-38, and 42-48 have been rejected on the ground that the specification, "while being enabling for treating lung cancer, does not reasonably provide enablement for treatment of all types of diseases of the instant claims." Claims 35-38 and 42-48 are directed to methods of treating CDK dependent proliferative disorders by administering a compound of formula I.

Applicants respectfully disagree with the Examiner's assessment that the specification does not reasonably provide enablement for treatment of the diseases claimed in the present application, other than lung cancer.

Applicants would like to direct the Examiner's attention to Example 19 (page 49) which clearly demonstrates that the compounds of the present invention have anti-proliferative (i.e., cytotoxic) effects against five different human tumor cell lines (c.f., Table 2). The human tumor cell line designation numbers are set out below accompanied by the biological source to which each cell line is related.

Human Tumor Cell Line	Source
A549	Lung
HeLa	Cervix
HT29	Colon
MCF7	Breast
Saos-2	Bone

Thus, the only cell line which corresponds to lung cancer is A549. The other cell lines disclosed do not relate to lung cancer but rather to cancers of the cervix, colon, breast, and bone.

With respect to the mode of action of the anti-proliferative compounds, Applicants would like to direct the Examiner's attention to page 14, line 26 to page 16, line 5 of the specification, where it is stated that the compounds of the present invention are delivered to exert their anti-proliferative effect in a non-protein kinase C (PKC) dependent manner. Furthermore, it is disclosed that many of the compounds inhibit cyclin-dependent kinase enzymes (CDKs) that have been shown to be involved in cell control.

With regard to the Examiner's allegation that tumor progression involves multiple mechanisms and that there is no single therapeutic approach in existence for the treatment of all tumors, Applicants respectfully maintain our argument that the skilled person would be able to determine which CDK dependent proliferative disorders could be treated with the anti-proliferative compounds of the present invention. It is disclosed in the specification that "an anti-proliferative effect within the scope of the present invention may be demonstrated by the ability to inhibit cell proliferation in an *in vitro* whole cell assay, for example using any of the cell lines A549, HT29, Saos-2, He-La or MCF-7, or by showing inhibition of a CDK enzyme (such as CDK2 or CDK4) in an appropriate assay" (page 15, lines 1-5). Both of these assays have been exemplified in the present case.

In addition, Example 17 describes experimental protocols by which the kinase specifity of a selected compound may be assayed. Thus, assays for CDK4/Cyclin D1, CDK2/Cyclin E, CDIK1/Cyclin B kinase may be carried out by monitoring the phosphorylation of GST-Rb. Alternatively, a CDK2/Cyclin A kinase assay can be conducted using recombinant CDK2/Cyclin A. In addition, Example 17 also discloses a suitable assay for the determination of PKCα kinase activity. The selectivity of various

compounds of the present invention for the inhibition of CDK2/Cyclin E is given in Table 1 on page 49 of the application as filed.

Therefore, Applicants submit that it would not be an undue burden for a person skilled in the art to determine which CDK proliferative disorders may be treated.

In addition, Applicants' claims are directed to methods of treating a subject for a CDK dependent proliferative disorder by administering a compound of the invention, such that the CDK dependent proliferative disorder is treated. Therefore, Applicants' claimed invention is directed ***only*** to methods wherein treatment of a CDK dependent proliferative disorder actually occurs after administration of the compound of the invention, and ***not*** to methods wherein treatment does not occur. Therefore, Applicants submit that the scope of the currently pending claims is fully enabled by the specification and respectfully request that this rejection of claims 35-38 and 42-48 be withdrawn.

Rejection of Claim 2 under 35 U.S.C. § 112, second paragraph

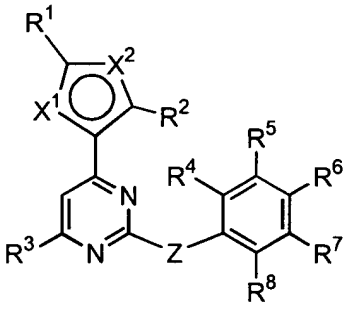
Claim 2 has been rejected under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly and distinctly claim the subject matter which Applicant[s] regard as the invention." In particular, the Examiner found there to be insufficient antecedent basis for the recital of the limitation that R^4-R^8 may be carbamoyl.

Applicants respectfully submit that this rejection no longer pertains to claim 2 as currently amended and respectfully request that this rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejection of Claims 1-2, 29, and 35-38 under 35 U.S.C. § 103(a)

Claims 1-2, 29, and 35-38 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Cao *et al.* (U.S. Patent Application No. 2003/0092714).

Claim 1 and its dependent claims are directed to compounds of the general formula I:



I

wherein:

X^1 is CR^9;

X^2 is NR^{10};

Z is NH;

R^1, R^2, R^3 R^9 and R^{10} are independently H, alkyl, aryl, aralkyl, heterocycle, halogeno, NO_2, CN, OH, alkoxy, aryloxy, (R''')nNH$_2$, (R''')nNH-R', (R''')nN-(R')(R''), NH-aryl, N-(aryl)$_2$, COOH, COO-R', COO-aryl, CONH$_2$, CONH-R', CON-(R')(R''), CONH-aryl, CON-(aryl)$_2$, SO_3H, SO_2NH_2, CF_3, CO-R', or CO-aryl, wherein alkyl, aryl, aralkyl and heterocycle groups may be further substituted with one or more groups selected from halogeno, NO_2, CN, OH, O-methyl, NH_2, COOH, CONH$_2$ and CF_3;

R^4, R^5, R^7, and R^8 are independently from each other H, substituted or unsubstituted lower alkyl, halogeno, NO_2, CN, OH, substituted or unsubstituted alkoxy, NH_2, NH-R', N-(R')(R''), COOH, COO-R', CONH$_2$, CONH-R', CON-(R')(R''), SO_3H, SO_2NH_2, or CF_3;

R^6 is H, substituted or unsubstituted lower alkyl, halogeno, NO_2, CN, OH, substituted or unsubstituted alkoxy, NH_2, NH-R', N-(R')(R''), COOH, COO-R', SO_3H, SO_2NH_2, or CF_3; wherein R' R'' and R''' are each independently alkyl groups that may be the same or different and n is 0 or 1; wherein at least two or three of R^1, R^2 and R^9 are not hydrogen or a pharmaceutically acceptable salt thereof. Claim 29 is directed to pharmaceutical compositions comprising a compound of claim 1.

Claim 35 is directed to a method for treating a CDK dependent proliferative disorder using compounds of claim 1.

According to the Examiner, "the reference teaches compounds of pyrimidyl compounds, see formula III' in page 10 wherein the Sp is a pyrrole and further the compound 1 (page 17) and compound 119 (page 27) in Table 1A...Since the instantly claimed compounds differ only by the positions of the substituents, they are positional isomers of the reference compounds. It would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are isomers of the reference compounds."

Applicants respectfully traverse this rejection. However, in order to expedite prosecution, Claim 1 as presently amended is directed to compounds of formula I wherein at least two or three of R^1, R^2 and R^9 are not hydrogen. The compounds of formula III-a (page 15, paragraph 212) as described in Cao are mono-substituted and do not correspond to compounds of formula I wherein at least two or three of R^1, R^2 and R^9 are not hydrogen. Cao does not teach or suggest the compounds presently claimed by Applicants in claim 1 or its dependent claims.

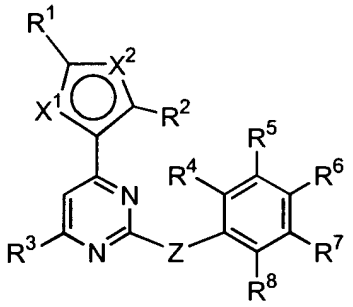
Therefore, Applicants respectfully request that this rejection of claims 1, 2 and 29, and 35-38 under 35 U.S.C. § 103(a) be withdrawn.

Rejection of Claims 40-41 under 35 U.S.C. §103(a)

Claims 40-41 were rejected under 35 U.S.C. § 103(a), as being unpatentable over Torley *et al.* EP 233 461.

Torley *et al.* describes the use of 4-(pyrrol-2-yl), 5, 6-substituted-2-pyrimidinamines for the treatment of pulmonary disorders, inflammatory disorders, allergic disorders, diabetes and cardiovascular disorders.

In claim 40, Applicants claim a compound of general formula I:



I

wherein:

X^1 is NH;
X^2 is CR^9;

Z is NH;

R^1, R^2, R^3 and R^9 are each independently selected from H, alkyl, aryl, aralkyl, heterocycle, halogeno, NO_2, CN, OH, alkoxy, aryloxy, $(R''')_nNH_2$, $(R''')_nNH$-R', $(R''')_nN$-(R')(R''), COOH, COO-R', $CONH_2$, CONH-R', CON-(R')(R''), SO_3H, SO_2NH_2, CF_3, and CO-R' wherein alkyl, aryl and aralkyl groups may be further substituted with one or more groups selected from halogeno, NO_2, CN, OH, O-methyl, NH_2, COOH, $CONH_2$ and CF_3;

R^4, R^5 and R^8 are each independently selected from H, halogeno, nitro, amino, aminoalkyl, hydroxy, alkoxy, carbamoyl, sulfamyl, N(R')(R''), C_{1-4} alkyl and substituted C_{1-4} alkyl;

R^6 is selected from H, halogeno, nitro, amino, aminoalkyl, hydroxy, alkoxy, carbamoyl, sulfamyl, N(R')(R''), butyl and substituted C_{1-4} alkyl;

R^7 is selected from H, halogeno, nitro, amino, aminoalkyl, hydroxy, carbamoyl, sulfamyl, N(R')(R'') C_{2-4} alkyl and substituted C_{1-4} alkyl;

wherein R' R'' and R''' are each independently alkyl groups that may be the same or different and n is 0 or 1, wherein at least two or three of R^1, R^2, and R^9 are not hydrogen, or a pharmaceutically acceptable salt thereof. Claim 41 is directed to pharmaceutical compositions comprising a compound of claim 40.

Applicants respectfully submit that Torley *et al.* fails to teach or suggest the compounds of claims 40-41, as currently amended. Applicants claim compounds wherein the pyrimidine is substituted by a pyrrol-3-yl group (e.g., compounds wherein X^1 is CR^9 and X^2 is NR^{10}), while in contrast Torley *et al.* only describes pyrimidine compounds substituted with a 2-pyrrolyl group. Furthermore, none of the compounds taught in Torley have di- or tri-substituted pyrrol radicals and, furthermore, Torley *et al.* fails to teach or suggest that these compounds would be useful in the treatment of CDK dependent proliferative disorders. Applicants respectfully submit that Torley *et al.* does not teach or suggest compounds of formula I, wherein at least two or three of R^1, R^2, and R^9 are not hydrogen.

Therefore, Applicants respectfully request that this rejection of the claims 40-41 under 35 U.S.C. § 103(a) be withdrawn.

Rejection of Claim 1-5, 9-11, and 29 under 35 U.S.C. § 103(a)

Claims 1-5, 9-11, and 29 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Torley *et al.* Claims 1-5, 9-11, and 29, and the disclosure in Torley *et al.* have been described above. Claim 1, as amended, relates to a compound of formula (I) in which the pyrrol radical is attached to the pyrimidine ring at the 3-position and has at least two or three of R^1, R^2 and R^9 are not hydrogen.

According to the Examiner, "the reference compounds have 2-position of the pyrrolyl group attached to the pyrimidine. The instantly claimed compounds on the other hand, have the pyrrolyl attached to the 3-position of the ring." Applicants disagree that the presently claimed compounds would have been obvious to the ordinarily skilled artisan for at least the following reasons.

Applicants note that the development of a molecular compound with a defined biological and chemical activity *in vivo* is a complex undertaking. The interaction between a substrate (i.e., pharmaceutical agent) and a target enzyme is not a trivial process.

A pharmaceutical agent affects an enzyme by binding to an active site in the enzyme. An important criterion for effective enzyme-substrate interaction is that the three dimensional shape of the substrate is complimentary to the three dimensional shape of the active site of the enzyme. A substrate which cannot adopt the necessary conformation either will not fit into the active site, or if binding is possible, may have a biological activity/toxicity different to that which was desired. Therefore, variations in the structure of a pharmaceutical agent (such as 3-subsituted versus 2-subsituted pyrrols) may have consequences on how that compound works *n vivo.*

Applicants submit that Torley *et al.* neither teaches nor suggests Applicants currently claimed compounds and requests that this rejection of the claims under 35 U.S.C. § 103(a) be withdrawn.

SUMMARY

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicant's Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,
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